PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P045248PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL 03/00703	International filing date *(day/month/year)* 17.10.2003	Priority date *(day/month/year)* 17.10.2002
International Patent Classification (IPC) or both national classification and IPC C12P21/00		
Applicant PHARMING INTELLECTUAL PROPERTY B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.05.2004	19.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Douschan, K Telephone No. +49 89 2399-8702

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00703

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 16,17,21,22

   because:

   ☒ the said international application, or the said claims Nos. 16,17,21,22 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8,9,13-15,17,19,21,22
	No:	Claims	1-7,10-12,16,18,20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-15,18-20
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 16, 17, 21 and 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 16, 17, 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
Since Claims 16, 17, 21 and 22 concern/comprise the application of a substance as or in a medicament, this is regarded as falling under the provisions mentioned above (see page 2 lines 26-30 of the description).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1). The documents mentioned in the International search report are cited by the following abbreviations:

D1: SCHOENBERGER, OEYVIND L.: "Characterization of carbohydrate chains of C1 - inhibitor and of desialylated C1 - inhibitor" FEBS LETTERS (1992), 314(3), 430-4, XP002268537
D2: EP-A-0 640 619 (AMGEN INC) 1 March 1995 (1995-03-01)
D3: WO 98/31826 A (BAYER ROBERT J ;CYTEL CORP (US); PAULSON JAMES C (US); SJOBERG ERI) 23 July 1998 (1998-07-23)
D4: WO 92/03149 A (BERLEX LAB) 5 March 1992 (1992-03-05)
D5: HARRISON, RICHARD A.: "Human C.hivin.1 inhibitor: improved isolation and preliminary structural characterization" BIOCHEMISTRY (1983), 22(21), 5001-7, XP002268538
D6: WO 01/57079 A (NUIJENS JOHANNES HENRICUS ;HEUS JORIS JAN

(NL); PIEPER FRANK R (NL) 9 August 2001 (2001-08-09)

D7: US-A-5 032 519 (ADLER BEVERLY ET AL) 16 July 1991 (1991-07-16)

D8: HARDUIN-LEPERS A ET AL: "1994, THE YEAR OF SIALYLTRANSFERASES" GLYCOBIOLOGY, IRL PRESS,, GB, vol. 5, no. 8, December 1995 (1995-12), pages 741-758, XP002913439 ISSN: 0959-6658

D9: WO 97/22347 A (WUILLEMIN WALTER ;HACK CORNELIS ERIK (NL); STICHTING CENTRAAL LAB) 26 June 1997 (1997-06-26)

Document D1 was erroneously cited as a P-document in the International search report. Nevertheless, D1 has been published already in 1992, so that it is clearly a prepublished document.

2). The **present patent application** concerns in claims 1-12 a C1 inhibitor which carries a modification of an O-linked carbohydrate, which results in a change of plasma circulatory half-life. This change can be an extension, which is achieved by either sialylation of the O-linked carbohydrate, or removal of one or more non-sialylated O-linked carbohydrates. A possible reduction of the plasma half-life is also mentioned (see claim 3 and description), but nowhere specified. All details given in the description (see e.g. p. 2 and 3) and the example (cf. p. 11) concern the extension of the plasma half-life by either sialylation ("capping") or removal of a O-linked carbohydrate, which results in a structure which interferes with the binding receptors involved in clearance and thus leading to a prolonged circulatory half life. **No explanation/example is given how to obtain the reduction of plasma circulatory half-life. This feature is therefore not regarded as being enabling.**

Claims 13-15 concern pharmaceutical preparations containing the modified C1 inhibitor.

Claims 16-22 are for a method for extending the blood circulatory half-life of a glycoprotein comprising compound, wherein one or more non-sialylated O-linked carbohydrates are removed from the glycoprotein. **Claims 16, 17, 21 and 22 are directed to/comprise *in vivo* methods (see point III above). Claims 16-21 are far too broad, since only C1 inhibitors are described in the description and the examples.**

3). **The prior art documents:**

D1 discloses on p. 433 the deglycosylation (partly or full) using an O-glycosidase. Although the changing of plasma half-life is not mentioned, the modified C1 inhibitors of claims 1-7 and 10-12 are nevertheless disclosed and therefore the said claims lack novelty. Since the modification of the O-linked carbohydrates is disclosed, D1 is relevant prior art for all claims of the present application with regard to inventive step.

D2 discloses the sialylation of the O-glycosylated part of a glycoprotein (erythropoietin) to increase its plasma half life (see especially p. 7 and claim 3 of D2). D2 is therefore a relevant document for the evaluation of inventive step for claims 1-15.

D3 is especially relevant on p. 8, 10, 11, 23-25 and discloses methods for the in vitro sialylation of glycoproteins which results in an increased therapeutic half life. Although it is not explicitly mentioned that O-linked carbohydrates are used, it is nevertheless implicit from p. 10. Pages 8 and 25 list a broad spectrum of possible substrates, showing that this modification can be performed with many glycoproteins and can be applied to further ones with great expectation for success. Pages 11 and 23 disclose enzymes also used in the present application. D3 is therefore a relevant document for the evaluation of inventive step for claims 1-15.

D4 discloses on p. 4 and 25 and claims 3-5 and 7 thrombomodulin analogs for pharmaceutical use with increased circulating half life. For this purpose partial or complete removal of O-linked sugar residues is performed. Therefore D4 is novelty destroying for claims 16, 18 and 20, and relevant for inventive step for all claims 1-22.

D5-D9 represent merely background literature.

4). **Novelty - Art. 33(1) and (2) PCT:**

As already discussed under item 3) above, the subject-matter of claims 1-7, 10-12, 16, 18 and 20 is already disclosed in the prior art documents D1 and D4, respectively, and therefore lacks novelty.

5). **Inventive step - Art. 33(1) and (3) PCT:**

Claims 1-7,10-12, 16, 18 and 20 lack novelty and therefore also the presence of an inventive step.

Claims 8, 9, 13-15, 17, 19, 21 and 22 are considered as being new, but nevertheless also lack an inventive step.

The specific enzymes mentioned in claims 8 and 9 are known to a skilled person as being suitable for the said purpose, therefore merely representing a preferred embodiment which either must lead itself to a surprising effect, or would be only inventive in combination with an inventive independent claim.

The pharmaceutical use claimed in claims 13-15 would only be inventive in combination with an inventive product.

The same objection applies to the subject-matter of claims 17, 19, 21 and 22.

Therefore, claims 8, 9, 13-15, 17, 19, 21 and 22 lack an inventive step in the light of D1-D4, either alone or taken in combination.

6). **Industrial applicability - Art. 33(1) and (4) PCT:**

The subject-matter of claims 1-15 and 18-20 is industrially applicable.